Knowledge from good, high quality, and valid studies, with enough information from which to make some sense, is awesome. It can come from meta-analyses, or randomised trials, or other studies of appropriate design. Look what *Bandolier* has been able to find for this month. Systematic reviews on three important topics, all of which provide answers to questions asked, sometimes frequently, sometimes not.

Of the frequently-asked variety, a systematic review of anti-obesity treatments examines trials of orlistat and sibutramine. What makes this interesting is that the review only included studies that lasted at least one year. Predictably some people had useful weight loss, though more gave up because of adverse events. Another example would be statin choice, and bang-for-buck in cholesterol lowering. Bucks are a variable feast, depending on where you live, but the bang is predictable.

Two more systematic reviews were found when trying to answer a question about B-type natriuretic peptide measurements and congestive heart failure. Any useful systematic review in diagnostic testing is amazing, so two was stunning. And both were useful. Here is the material for making policy decisions, and it is just a moment away with a little searching. As was trying to figure out what evidence existed for coxibs and dysmenorrhoea, to supplement the evidence on NSAIDs in *Bandolier* 120.

And finally, in trying to help us to help ourselves, there is a randomised trial of lifestyle modification to lower blood pressure. It worked, with fewer participants with hypertension and more with optimum blood pressure after six months. The flies in the ointment were that the study was longer than six months, but chose six month outcomes (because of clinical guideline decisions), and the old one of cost judgement in particular circumstances.

Bandolier in bulk

A reminder that although the cost of individual subscriptions to *Bandolier* runs at £36 a year (£72 overseas because of higher administrative and postage costs), bulk costs are way lower. For instance, bulk delivery of *Bandolier* to any organisation in the UK brings the individual cost way down for 50 copies per month. Even less for more. With large savings of over two thirds, it is possible to have more people thinking about evidence for quite respectable outlays. Worth a thought. Overseas readers should note that imaginative ways are possible for bulk purchase outside the UK.

CHOLESTEROL LOWERING

WITH STATINS

Cholesterol-lowering drug prescriptions have increased seven fold in the last five years in the UK, with statins accounting for 92% of prescriptions and 95% of cost (about £350 million a year in 2001). Simvastatin (43%) and atorvastatin (32%) are the most commonly prescribed. Long-term benefits are reduced heart attacks and strokes, and the new Statin section on the *Bandolier* Internet site has summarised the evidence about benefit and harm from statins. What about knowing which dose gives best lipid lowering in long-term trials? A new systematic review [1] gives the answer.

Systematic review

Searching for randomised, double-blind controlled trials assessing the effect of statins on cholesterol in patients with hypercholesterolaemia was to September 2001, using the Cochrane Library and PubMed. Pharmaceutical companies known to manufacture statins were contacted for references. Reference lists of retrieved trials and reviews were checked to identify other studies.

Included trials were both randomised and double blind, had at least two treatment groups (placebo, different doses of the same statin, or different treatments), had a mean total cholesterol of at least 5.0 mmol/L at baseline (with or without dispersion), and provided baseline and outcome data for total cholesterol, LDL, HDL and triglycerides. Only those of at least three months were included, because trials of less than three months duration are unlikely to inform adequately about sustainable effects in terms of lipid lowering with statins.

Studies without baseline data were excluded, as were those with fewer than 20 patients per treatment group. Also ex-

cluded were trials with mean baseline concentration of total cholesterol below 5.0 mmol/L, combinations of a statin plus another drug, trials examining patients with familial hypercholesterolaemia, diabetes mellitus, renal or hepatic pathology, or trials in which patients were randomised to statin treatment within 24 hours of procedures such as angioplasty or cardiac surgery.

The main outcomes sought were mean change (absolute or percent) from baseline during double blind treatment for total cholesterol, LDL, HDL and triglycerides, or data allowing their calculation.

Results

Forty-two reviews and 509 reports regarded as potential randomised trials were retrieved, and 418 were excluded, mostly because they were shorter than 12 weeks, were not double blind, had fewer than 20 patients per group, or were duplicates. Ninety-one trials met the inclusion criteria and contributed to the analysis, with 43,404 patients on statins and 25,081 on placebo. In most trials initial average concentration of total cholesterol was between 6.5 and 7.8 mmol/L.

Most patient information was available for lovastatin, pravastatin and simvastatin, mainly because of the publication of large, long-term trials, with far less information available for atorvastatin, cerivastatin, fluvastatin and rosuvastatin. The most commonly used doses were atorvastatin 10 mg, fluvastatin 40 mg, lovastatin 40 mg, pravastatin 40 mg and simvastatin 40 mg. Information for both 5 mg and 10 mg of rosuvastatin was used since patient numbers were almost identical.

Neither duration of study beyond 12 weeks, nor initial concentration of cholesterol, nor use of placebo or active con-

Figure 1: Percentage change in LDL-cholesterol from baseline with different simvastatin doses
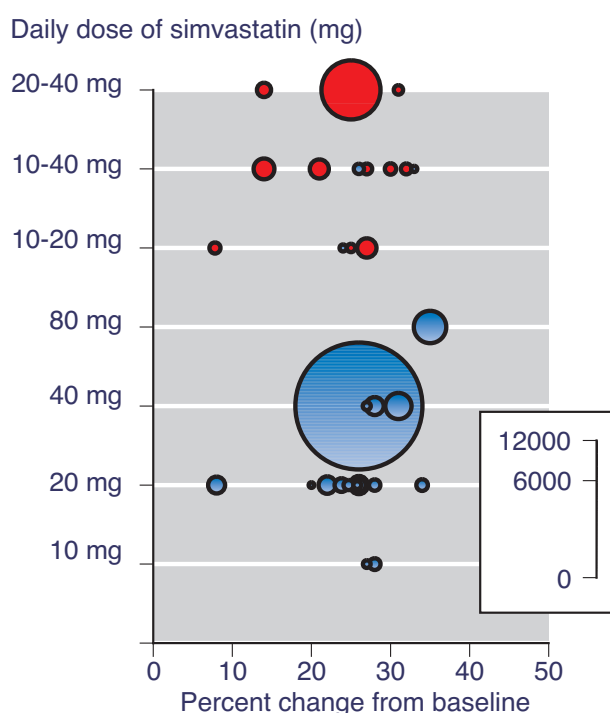

Figure 2: Percentage change in total cholesterol from baseline (number of subjects)
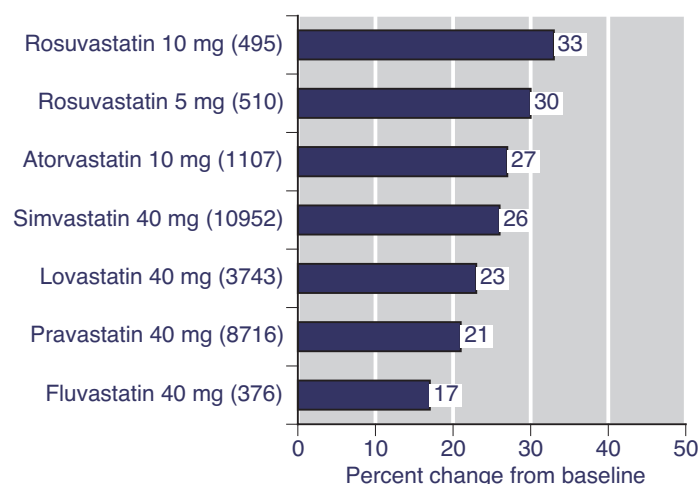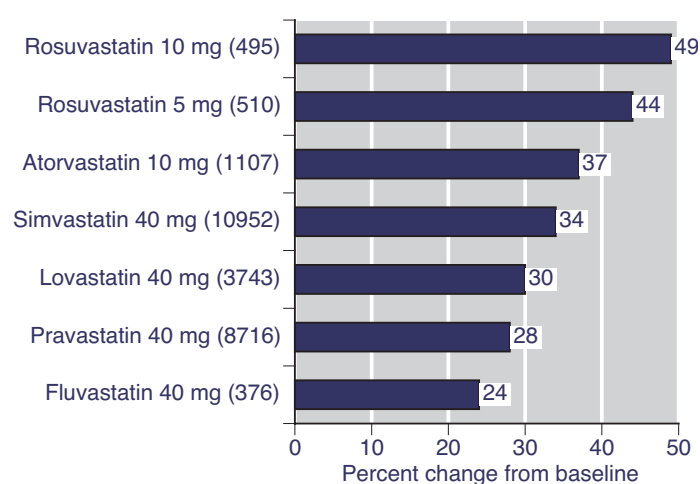

Figure 3: Percentage change in LDL-cholesterol from baseline (number of subjects)

trols, nor the inclusion or exclusion of major trials had any effect on lipid-altering capacity. The cholesterol-lowering capacity of statins was generally unaffected by dose used, or by use of fixed dose or dose-titration. Figure 1 shows this for the statin with the largest amount of information, simvastatin.

The cholesterol-lowering capacity of the most commonly used fixed doses was different between statins. Figure 2 shows the mean percentage reductions for total cholesterol, and Figure 3 for LDL-cholesterol. In both cases the rank order was the same, with 5 and 10 mg of rosuvastatin giving the largest reduction, and the two most prescribed statins ahead of the all other statins.

The all cause discontinuation rate was about 10% and discontinuation because of adverse events was about 4% in these trials, with no major difference between statins.

Comment

So what are the take-home messages? One is that in the UK, and probably world wide, prescribing of statins has been evidence-based, since the most frequently used (atorvastatin 10 mg and simvastatin 40 mg) are the established statins with the most cholesterol-lowering impact.

That is encouraging. Rosuvastatin, with less information, seems to have even more punch at 5 mg and 10 mg. This might help costing exercises based on local pricing regimes, though arguments about effects of statins above those of cholesterol lowering will probably continue.

Even so, it was surprising that there was only information on about 1,000 patients for atorvastatin and rosuvastatin, compared with 11,000 for simvastatin. The cholesterol-lowering effect for atorvastatin in the large ASCOT study [2] is in line with the effect found in the meta-analysis.

Perhaps the most surprising thing was the lack of dose response in these longer term studies. Law and colleagues [3] analysed trials of two to six weeks duration by drug and dose in 25,000 patients on statins and found good dose-response for all statins. This new meta-analysis [1] had data from 68,000 patients but in trials lasting 12 weeks or more. This may reflect better the long term use of statins, and if so may open a question about how long people should be on a statin before dose or drug change is considered. *Bandolier* could find no papers that looked at how long it took for the maximum reduction in cholesterol to be achieved.

References:
1 JE Edwards, RA Moore. Statins in hypercholesterolaemia: A dose-specific meta-analysis of lipid changes in randomised, double blind trials. BMC Family Practice 2003, 4:18.
2 PS Sever et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a multicentre randomised trial. Lancet 2003; 361: 1149-1158.
3 MR Law et al. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003 326: 1423-1429.

LIFESTYLE MODIFICATION AND BLOOD PRESSURE

Lifestyle is the new pink (or black, or whatever). Even governments now witter on about reducing obesity, changing diet, and increasing exercise. That is a wonderful thing to see, but a problem can sometimes be that ordinary folk may not know which part of the message to concentrate on. Should I lose weight, or reduce my salt intake? Take more exercise, or eat more fruit? The answer is that comprehensive lifestyle modification is the key to getting on top of moderately raised blood pressure [1]. *Bandolier* has always had a dread of antihypertensive medicines, so knowing that a batch of changes can keep them at bay makes good reading.

Study

Participants in this randomised study were generally healthy adults with above optimal blood pressure, and included people with mild hypertension and who were not taking antihypertensive medicines. The systolic BP had to be between 120 and 159 mmHg, and the diastolic BP between 80 and 95 mmHg as a mean over three screening visits. They were 25 years of age or older, and had a body mass index between 18.5 and 45 kg/sq metre. Excluded were those taking drugs likely to affect blood pressure, and people who drank more than 21 units a week, or who had major medical conditions.

Randomisation was to:
♦ An advice only group with a single 30 minute period of instruction.
♦ A behavioural intervention, termed "established" that implemented traditional lifestyle changes with a target of 18 face-to-face interviews over six months with aims of weight loss (at least 7 kg for those with a BMI over 25), at least three hours of moderate to intense physical activity a week, limitation of dietary sodium to no more than 100 mEq daily, and reducing alcohol intake to two drinks a day for men and one for women.
♦ The behavioural intervention plus the use of the DASH (Dietary Approaches to Stop Hypertension) diet. This diet has been shown to reduce BP particularly in those with intermediary or high salt intakes. The DASH diet emphasises fruit, vegetables and low-fat dairy foods; includes whole grains, poultry, fish and nuts; contains smaller amounts of red meat, total and saturated fat, cholesterol and sugar; and larger amounts of potassium, calcium, magnesium, dietary fibre and protein, compared with a typical diet. As such it is not just a diet for people trying to prevent or treat high blood pressure. It is a healthy diet that everyone should be recommended to follow.

The main outcome was blood pressure measured at six months, though many other outcomes were measured by personnel masked to randomisation assignment.

Results

There were 810 participants with a mean age of 50 years and BMI of 33 kg/sq metre, of whom 62% were women and 34% African American. The mean initial systolic blood pressure was 135 mmHg, and diastolic 85 mmHg, with 38% hypertensive (defined as a blood pressure over 140/90 mmHg). Participants in the three groups were well matched at baseline. The majority of patients (70-80%) attended at least 15 of the 18 planned sessions in the active intervention groups.

Blood pressure declined in all three groups over the six months. In the advice-only group the mean reduction in systolic BP was 7 mmHg, and 11 mmHg in both intervention groups. Diastolic BP reductions were 4 mmHg and 6 mmHg respectively. The interventions made the expected changes, with more weight loss (5-6 kg) in the intervention than advice group (1 kg). Participants in the established + DASH group ate more fruit and vegetables, less fat, and less saturated fat, so the interventions could be seen to achieve their dietary goals.

Figure 1: Participants with hypertension or optimum blood pressure
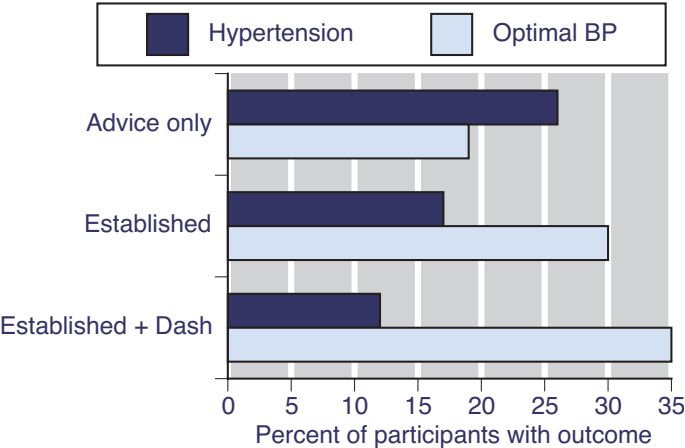
Most interesting was the proportion of participants who, at six months, were hypertensive (BP greater than 140/90 mmHg) or who had optimal BP, at 120/80 mmHg or below). Figure 1 shows that the best results, with most participants with optimal BP and fewest who were hypertensive occurred with established + DASH, and Table 1 shows the numbers needed to treat to achieve these outcomes.

Behavioural modification plus the DASH diet had numbers needed to treat of 7 (95% CI 5 to 13) to prevent one participant being hypertensive, and 6 (4 to 12) for one participant to have optimal BP. Only one in four of those with blood pressure above 140/90 mmHg still had this degree of elevation after six months of behavioural modification plus the DASH diet, compared with one in two with advice only.

Comment

Behavioural modification plus the DASH minimised the extreme results we don't want (hypertension) and maximised the extreme result we do want (optimal blood pressure). These are substantial and important results for healthcare systems and individuals. For individuals, the message is that reducing weight and salt, and increasing exercise and consumption of fruits and vegetables can keep us from needing to see our doctors, except socially. For healthcare systems, the results highlight a concerted way in which prevention can keep patients away from expensive and possibly harmful medicines, and perhaps reduce cost while improving peoples' health.

Reference:
1   Premier Collaborative Research Group. Effects of comprehensive lifestyle modification on blood pressure control. JAMA 2003 289: 2083-2093.

Table 1: NNTs for active therapy versus advice only

Outcome and comparison	NNT 95%CI)
Prevent hypertension	
Established vs advice	11 (5 to 55)
Established + DASH vs advice	7 (5 to 13)
Promote optimum BP	
Established vs advice	9 (5 to 29)
Established + DASH vs advice	6 (4 to 12)

COXIBS FOR DYSMENORRHOEA

Bandolier 120 looked at a systematic review [1] of NSAIDs for dysmenorrhoea, and the question arose about effectiveness of newer coxibs. A search found four randomised trials and the results appear below, but these coxib trials differed from the NSAID trials in the outcomes used, so a brief digression into trial designs is needed before we get to the results.

Pain with dysmenorrhoea usually lasts for about three days, though with considerable individual variation. Trials of analgesics can have various forms. The simplest might be to give the same analgesic for the whole of the painful cycle, and ask a global question concerning efficacy at the end. Women might then be crossed over to a different treatment at the next cycle. This was the design used for NSAID comparisons with placebo, with the outcome of at least moderate pain relief over the cycle.

A variation would be to use the same basic structure, but make more detailed evaluations of pain or pain relief over a limited time during the first day. This was the approach used in the coxib trials.

Coxib trials

Bandolier searched PubMed for randomised trials comparing any coxib (celecoxib, etoricoxib, lumaricoxib, rofecoxib, valdecoxib) with placebo or analgesic in women with painful dysmenorrhoea. Four published trials [2-5] were found (Table 1). All investigated the analgesic efficacy of a first dose in women with moderate or severe menstrual pain. All included both placebo and naproxen sodium 550 mg. Three were double blind, and one [3] was an open study that also had a global outcome over the cycle, but compared with once-daily naproxen sodium 550 mg, rather than the usual dose of twice daily naproxen.

Results

Over the first 8-24 hours, all analgesics were better than placebo, but there was no difference between coxibs and naproxen sodium 550 mg for any analgesic measurement, or use of additional analgesic therapy. Only one trial [4] provided a patient outcome of good or excellent response over 12 hours, which gave numbers needed to treat compared with placebo of about 3 for naproxen sodium 550 mg and valdecoxib 40 mg, and 4 for valdecoxib 20 mg. Over a cycle in the open trial [3] both 25 mg and 50 mg daily rofecoxib was better than naproxen sodium 550 mg.

Adverse events did not differ between groups, though a very high rate of gastrointestinal adverse events (64%) was reported for naproxen sodium in the open trial [3]. Discontinuations were infrequent.

Comment

There were 285 women in these four studies, almost all of whom had both placebo and naproxen sodium 550 mg. This is more than the 180 or so women in trials of naproxen and

Table 1: Individual randomised trials comparing a coxib with placebo and/or NSAID in dysmenorrhoea

Reference	Design	Treatments (women)	Outcomes	Results
Morrison et al, 1999	Randomised, double blind, comparison of rofecoxib 25 and 50 mg, naproxen sodium 550 mg and placebo. First dose efficacy, crossover between menses in 127 women	Placebo (118) Rofecoxib 25 mg (115) Rofecoxib 50 mg (118) Naproxen sodium 550 mg (122) First dose, then every 12 hours as needed (once daily rofecoxib 25 mg, twice daily naproxen)	Pain relief and intensity over first 8 hours Peak relief Additional medication in first 12 hours Additional analgesia in 12-72 hours	All active better than placebo, except additional analgesics taken 12-72 hours No difference between analgesics No adverse event difference, and no serious adverse events
Sahin et al, 2003	Randomised, open comparison of rofecoxib 25 and 50 mg, naproxen sodium 550 mg and placebo. First dose efficacy, crossover between menses in 55 women	Placebo (55) Rofecoxib 25 mg (55) Rofecoxib 50 mg (55) Naproxen sodium 550 mg (55) First dose, then once daily as needed	Pain intensity over first 24 hours Overall analgesic efficacy score over the cycle Pill count	All active better than placebo for pain intensity "Perfect" global efficacy in 90% with rofecoxib (both doses), and 33% with naproxen Total pills taken lower for rofecoxib than placebo 64% gastrointestinal adverse events for naproxen
Daniels et al, 2002	Randomised, double blind, comparison of valdecoxib 20 and 40 mg, naproxen sodium 550 mg and placebo. First dose efficacy, crossover between menses in 30 women	Placebo (29) Valdecoxib 20 mg (30) Valdecoxib 40 mg (30) Naproxen sodium 550 mg (29) First dose, then twice daily as needed	Pain relief and intensity over first 8 and 12 hours Global assessment at 12 hours Additional medication in first 12 hours	All active better than placebo, except additional analgesics taken over 12 hours, where both valdecoxib doses but not naproxen had fewer than placebo No difference between analgesics No adverse event difference
Malmstrom et al, 2003	Randomised, double blind, comparison of etoricoxib 120 mg, naproxen sodium 550 mg and placebo. First dose efficacy, crossover between menses in 73 women	Placebo (73) Etoricoxib 120 mg (73) Naproxen sodium 550 mg (73) First dose only	Pain relief and intensity over 24 hours Analgesia onset Peak relief Additional medication in first 12 hours	Both active treatments same, and better than placebo for relief over first 8 hours, and other outcomes. No adverse event difference, and no serious adverse events

placebo in the systematic review of NSAIDs [1], so these four trials constitute an important addition to knowledge, even if one of them was open. They all come up with the same answer, namely that coxibs at standard doses are equivalent to naproxen sodium 550 mg over eight to 12 hours after the first dose at the onset of menstrual pain.

These outcomes are, of course, important for regulatory authorities, but are less helpful for every day consideration, though once-daily dosing for some coxibs is a theoretical benefit. What was missing was more woman-centred outcomes, and, also, information on adverse events over a cycle, in sufficient numbers of women to spot a difference. Were these outcomes actually captured in the trials, but not reported because they are of little interest to regulatory agencies? It would be fascinating to know. So while we move on a bit, we have still to make the great leap forward.

References:
1   J Marjoribanks J et al. Nonsteroidal anti-inflammatory drugs for primary dysmenorrhoea (Cochrane Review). In: the Cochrane Library, Issue 4, 2003.
2   BW Morrison et al. Rofecoxib, a specific cyclooxygenase-2 inhibitor, in primary dysmenorrhoea: a randomized controlled trial. Obstetrics & Gynecology 1999 94:504-508.
3   I Sahin et al. Dysmenorrhea treatment with a single daily dose of rofecoxib. International Journal of Gynecology & Obstetrics 2003 83: 285-291.
4   SE Daniels et al. Valdecoxib, a cyxlooxygenase-2-specific inhibitor, is effective in treating primary dysmenorrhoea. Obstetrics & Gynecology 2002 100:350-358.
5   K Malmstrom et al. Analgesic efficacy of etoricoxib in primary dysmenorrhea: results of a randomized, controlled trial. Gynecologic and Obstetric Investigation 2003 56: 65-69.

ANTI-OBESITY DRUGS REVIEWED

How well do anti-obesity drugs work? Interesting question, this, and one asked by a number of readers. *Bandolier* had spent a few hours beginning to wonder about whether to do a brief review, when happily a really good one arrived [1]. The short answer is that in long term studies of a year or more these drugs achieved weight loss of 3-4% more than doing nothing, or with diets.

Systematic review

The review searched for studies in four databases, reference lists, and reviews, and asked experts and companies for help. Only double blind, randomised trials of at least one year were acceptable. They had to enrol patients with a BMI of at least 30 kg/sq metre, and have a placebo or active control. Full, published studies in any language were accepted.

The primary outcome was average weight loss, both in kg and as percentage change from baseline, and the dichotomous outcomes of the percentage of patients with at least 5% or at least 10% weight loss.
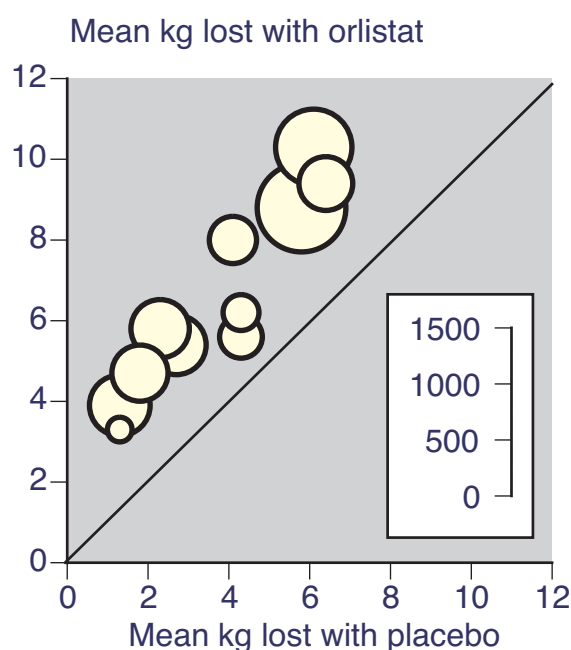
Results

Only 11 studies of orlistat (6,021 participants) and three of sibutramine (929 participants) met the inclusion criteria. All of the orlistat trials had co-interventions that typically included dietary counselling and education, as well as encouragement to exercise, and in nine of the studies participants used a deficit diet as well. In one of the sibutramine studies participants were given dietary advice sheets.

Most studies had a preponderance of women (70-80%) with an average age of about 50 years. Many of the trials enrolled higher risk populations with diabetes and cardiovascular risk factors. The studies had very high withdrawal rates, averaging 33% for orlistat and 43% for sibutramine. Most trials dealt with this by imputing a last observation carried forward analysis.
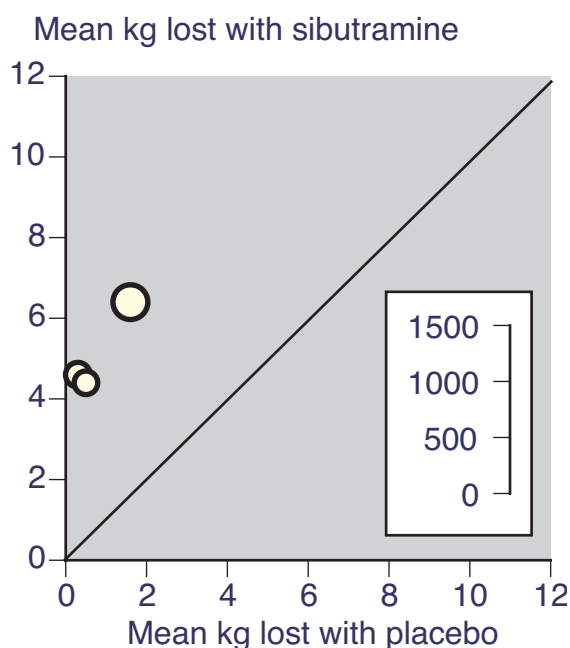
Figure 1: Trials of orlistat versus placebo

Weight loss

Orlistat 120 mg three times a day for a year or more produced a consistent reduction in weight above that of placebo (Figure 1) by an average of 2.7 kg or 2.9% of initial weight. Compared with placebo 21% of patients (NNT 5) had at least a 5% weight loss and 12% (NNT 10) achieved a 10% weight loss.

Sibutramine 15-20 mg daily for a year or more produced a consistent reduction in weight above that of placebo (Figure 2) by an average of 4.3 kg or 4.6% of initial weight. Compared with placebo 34% of patients (NNT 3) had at least a 5% weight loss and 15% (NNT 7) achieved a 10% weight loss.

Table 1: Summary of outcomes of all trials of orlistat or sibutramine versus placebo lasting at least one year

Outcome	Trials	Patients	Weighted mean difference (active - placebo) (95% CI)	NNT 95% CI
Orlistat				
Weight loss (kg)	11	5473	2.7 (2.3 to 3.1)	
Weight loss (%)	10	4941	2.9 (2.3 to 3.4)	
5% responders	11	5473	21 (19 to 24)	5 (4 to 5)
10% responders	10	4941	12 (8 to 16)	10 (6 to 13)
Sibutramine				
Weight loss (kg)	3	738	4.3 (3.6 to 4.9)	
Weight loss (%)	3	738	4.6 (3.8 to 5.4)	
5% responders	3	738	34 (28 to 40)	3 (2.5 to 3.6)
10% responders	3	738	15 (4 to 27)	7 (4 to 25)

Figure 2: Trials of sibutramine versus placebo

Mean kg lost with sibutramine (y-axis, 0 to 12) versus Mean kg lost with placebo (x-axis, 0 to 12). Legend shows bubble sizes: 1500, 1000, 500, 0.

Adverse events

Gastrointestinal adverse events predominated with orlistat, and included fatty / oily stool, faecal urgency, and oily spotting in 15% to 30% of patients. Faecal incontinence occurred in 7% of those on orlistat compared with 1% on placebo, a number needed to harm of 17.

Sibutramine adverse events included increases in systolic and diastolic blood pressure of 1-3 mmHg, and pulse rate increases of 4-5 beats per minute. Other adverse events such as insomnia, dry mouth, nausea and constipation occurred in 7-20%.

Comment

A minority of patients achieved a 10% or greater weight loss, which is a useful amount. It is also a more useful trial outcome than average weight loss, since the heavy contamination of later data by imputed values from patients who had withdrawn will probably make those results unreal. An interesting discussion for another occasion is the legitimacy of imputing missing value data, both how much is reasonable (a little may be, but a lot not) and how it is done (is last observation carried forward always legitimate?).

The authors of the review comment that there were no predictive factors for responders, and suggested that therapeutic trials made sense because many patients would stop because of adverse events, while the near maximal weight loss was usually seen in the individual studies by six months. The bottom line is that weight reducing drugs are of value in a few, with significant adverse events in many.

Reference:
1   R Padwal et al. Long-term pharmacotherapy for overweight and obesity: a systematic review and meta-analysis of randomized controlled trials. International Journal of Obesity 2003 27: 1437-1446.

BNP FOR CHF

Diagnostic tests are a problem. The explosion of substances found to influence cellular behaviour seems to be rolling on remorselessly. When we learn how to measure them, we find that most of these substances can be found in body fluids like blood, urine, or cerebrospinal fluid. And because they can be measured, people measure them. They will inevitably find that concentrations are higher in some people than others, perhaps people with different conditions, and a diagnostic test is born.

New-born diagnostic tests are weak and feeble creatures. They will have been tested on a few selected people, often compared in people with the most advanced condition and healthy youngsters in the laboratory. A bit of spin and the weak and feeble test comes roaring though the literature, and is the latest craze.

That overstates it, but it is certainly the case that knowing in whom to use a new diagnostic test is difficult, and the interpretation uncertain. So where are we with B-type natriuretic peptide (BNP), the new kid on the block for use in heart failure? Luckily we already have two systematic reviews [1 2] to help, and their underlying message is that the test may well be helpful, but we need strategies in place to use it properly.

Background

BNP is a cardiac neurohormone secreted from the ventricles in response to volume expansion and pressure overload, though some is also released from atrial tissue. BNP gene expression increases rapidly in response to stimulus. BNP is a 32 amino acid peptide, and is measured using the N-terminal, and assays generally measure both intact and N-terminal BNP, and there is uncertainty about whether measuring both or either is better.

BNP for CHF diagnosis

Four studies of reasonable quality have compared BNP measurements with echocardiogram as a reference diagnostic standard in appropriate patients with New York Heart Association classes I-IV heart failure using independent blind comparison. In all, about 2,200 patients were studied, with the largest group of patients (almost 1,600) presenting to an emergency room with dyspnoea. Some of the studies were using point-of-care BNP tests.

In the largest study about half (49%) did not have congestive heart failure, and most had BNP levels under 100 ng/L. In those with heart failure, concentrations rose with severity (Table 1). Note the very large standard deviations in Table 1, showing great variability.

Table 2 shows the diagnostic performance of the four studies. Positive likelihood ratios were as high as 40, and as low as 4. Even so, a likelihood ratio of four for a positive test, starting with a 50% prevalence, would produce a post-test probability of about 80%, and the likelihood ratio of a negative test of 0.1, a post test probability of about 8%. How

Table 1: BNP concentrations with increasing CHF severity

NYHA Class	Mean ± SD (ng/L)
I	240 ± 290
II	390 ± 370
III	640 ± 450
IV	820 ± 440

Figure 1: Characteristics of BNP test applied to a hypothetical 1,000 people attending an emergency room with dyspnoea and suspected CHF
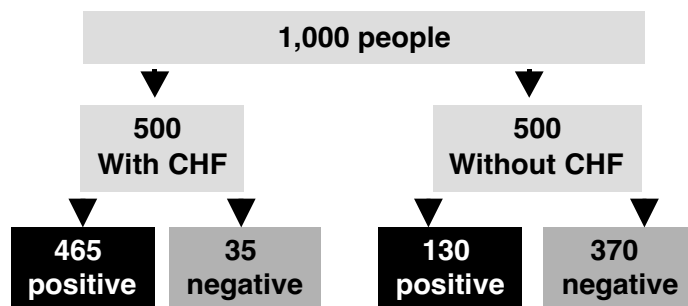
these figures for the worst result from the largest study look in natural frequencies is shown in Figure 1, using a cut off of 80 ng/L. Below a lower cut-off of 50 ng/L, 96% of all results would have correctly predicted that a patient did not have congestive heart failure, effectively ruling out the diagnosis.

BNP for prognosis

Two studies of reasonable quality demonstrated that lower BNP concentrations correlated with better outcomes, and higher values with worse outcomes.

BNP for monitoring

Two small studies suggested that better treatment produced lower BNP concentrations, and that BNP-guided therapy resulted in significantly fewer cases of cardiovascular death, admission, or outpatient attendance.

Comment

A reader, who wanted to know whether this was a useful test in primary care, alerted *Bandolier* to BNP as an issue. The straight answer is that as it stands there just isn't a satisfactory answer, beyond the rather trite one of there not

being enough evidence. But a test is just a tactic. What is missing is a strategy.

The two systematic reviews are incredibly helpful in setting out the background. They reflect their origins, one from a department of family and community medicine [1], and the other from a cardiovascular research centre [2]. Both are positive, and the evidence around BNP as a marker of heart failure is good, so far as it goes. But there are unknowns. For instance, is it likely that the test will be done in primary care offices and surgeries where a patient first presents? Unlikely in most places. More likely will be its use in hospital outpatients or emergency rooms, but even there close cooperation between physicians and laboratories will be needed.

Both the reviews tell us how difficult it is to diagnose heart failure, with references to prove it. They hint at strategies involving clinical examination, X-rays, and BNP measurements, and emphasise the other things that can elevate BNP, like myocardial infarction, ventricular hypertrophy, cardiomyopathy, lung cancer, pulmonary embolism, renal failure, and COPD. We can predict that BNP is no holy grail of testing, but it is probably going to be useful. The challenge is to work out how.

And a quick postscript. There is talk of using the test to screen for heart failure. No one has yet tried it, and it will be fraught.

References:
1   R Cardarelli, TG Lumicao. B-type natriuretic peptide: a review of its diagnostic, prognostic, and therapeutic monitoring value in heart failure for primary care physicians. Journal of the American Board of Family Practice 2003 16: 327-333.
2   JA de Lemos et al. B-type natriuretic peptide in cardiac disease. Lancet 2003 362: 316-322.

Table 2: Characteristics of BNP testing in four different studies

Study	Patients	BNP cut-off ng/L	Sensitivity %	Specificity %	Positive likelihood ratio
1	122	76	97	84	6
2	250	80	98	92	12
3	1586	80	93	74	4
4	321	94	86	98	43